REMARKS

Claims 11-19 and 21-31 are pending in this application. Non-elected claims 12, 14-16, 18, 19, 21, 22, 24, 25, 27, 28, 30 and 31 have been withdrawn from consideration by the Examiner.

In view of the following remarks, reconsideration and allowance are respectfully requested.

I. Rejection Under 35 U.S.C. §103

The Office Action rejects claims 11, 13, 17, 23, 26 and 29 under 35 U.S.C. §103(a) as having been obvious over U.S. Patent No. 6,686,505 to Watanabe et al. ("Watanabe") in view of JP 11-189600 to Ikariya et al. ("Ikariya"). Applicants respectfully traverse the rejection.

Claim 11 requires that hydrogenation of the ketone compound occurs "without the presence of a base" and in the presence of "pressurized hydrogen" (hydrogen gas). The combination of references would not have rendered obvious the claimed process for at least the following reasons.

The applied references do not disclose hydrogenation of the ketone compound in the absence of a base because both references disclose a ruthenium chloride catalyst that hydrogenates ketones in the presence of a base. Ikariya discloses ruthenium dichloride catalysts that are converted into an active catalyst in the form of a dihydride complex. See Ikariya, examples 11-15; see also Abdur-Rashid at page 2656, column 1, paragraph 1; and Ohkuma I at page 2675.[1] Ketones are asymmetrically reduced by this dihydride complex in the presence of a base, such as KOH and KO-t-Bu. Id.

Watanabe also discloses a chloride catalyst that hydrogenates ketones in the presence of a base. The Office Action asserts that Watanabe teaches the use of the claimed catalyst in

[1] Abdur-Rashid et al., *Organometallics*, 2000, 19 (14), 2655-2657 (Abdur-Rashid is attached for the Examiner's convenience). Ohkuma et al., *J. Am. Chem. Soc.*, 1995, 117, 2675-2676 (Ohkuma I is attached for the Examiner's convenience).

the presence or absence of a base. See Office Action at page 3. However, there is no evidence that the specific process of Watanabe could be practiced without using a base or that an ordinarily skilled artisan would understand Watanabe to be teaching such in a general manner. Instead, the evidence is to the contrary.

Watanabe, in examples 1-4, discloses a ruthenium chloride catalyst RuCl (Tsdpen)(p-cymene). Ohkuma II discloses that in order for this particular catalyst to perform asymmetric hydrogenation of ketone, it must be first converted into an amide complex by treatment with a strong base, which is then converted into a monohydride complex to form the active catalyst species. See Ohkuma II at page 8724.[2] Furthermore, examples 1-4 of Watanabe disclose the use of a base, i.e., triethylamine, in the asymmetric reduction step. One of ordinary skill in the art would understand that a ruthenium chloride catalyst should be treated with a base to form the active catalyst species used for hydrogenation of ketones. Thus, the combination of references does not disclose the hydrogenation of ketones by a chloride complex "without the presence of a base."

Additionally, there exists no reason or rationale for one of ordinary skill in the art to modify Watanabe to use the hydrogen gas disclosed by Ikariya because the active catalyst species derived from the ruthenium chloride catalyst of Watanabe was not known to activate hydrogen gas as a hydrogen source to hydrogenate ketones. As discussed above, Watanabe discloses a ruthenium chloride catalyst, which is converted into an active catalyst in the form of a monohydride complex. See Watanabe, examples 1-4. This active catalyst species activates a hydrogen donor to asymmetrically reduce ketones. Id. Watanabe does not disclose that the active catalyst species can activate hydrogen gas.

---

[2] Ohkuma et al., *J. Am. Chem. Soc.*, 2006, 128 (27), 8724-8725 (Ohkuma II is attached for the Examiner's convenience).

In fact, it was thought in the prior art that hydrogenating ketones using hydrogen gas as a hydrogen source was impossible regardless of the presence or absence of a base. See Fujii at page 2522, right column, lines 22-24 (describing that hydrogen gas contributes little to the generation of alcohol, and that a reaction using hydrogen gas/acidic acid gives a poor yield of 5% and an asymmetrical yield of 75% ee).[3] Thus, one of ordinary skill in the art would not have used hydrogen gas with the ruthenium chloride catalyst of Watanabe, which cannot activate hydrogen gas, to hydrogenate ketones with any expectation of success, let alone a reasonable expectation of success.

Thus, Watanabe and Ikariya would not have rendered obvious claim 11. Claims 13, 17, 23, 26 and 29 depend from claim 11 and, thus, also would not have been rendered obvious by Watanabe and Ikariya for at least the same reasons. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 11-19 and 21-31 are earnestly solicited.

[3] Fujii et al., *J. Am. Chem. Soc.*, 1996, 118, 2521-2522 (Fujii is attached for the Examiner's convenience).

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

James A. Oliff
Registration No. 27,075

Tommy T. Kim
Registration No. L0543

JAO:TTK/emd

Attachments:
Abdur-Rashid
Ohkuma I
Ohkuma II
Fujii

Date: November 12, 2009

OLIFF & BERRIDGE, PLC
P.O. Box 320850
Alexandria, Virginia 22320-4850
Telephone: (703) 836-6400

DEPOSIT ACCOUNT USE AUTHORIZATION
Please grant any extension necessary for entry;
Charge any fee due to our Deposit Account No. 15-0461

D3

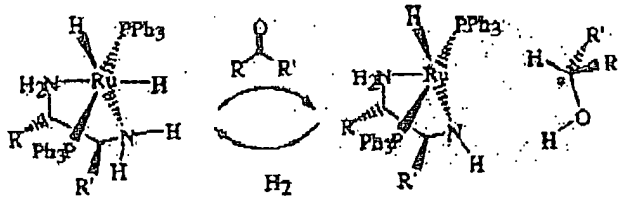
ORGANOMETALLICS

Communication

Ruthenium Dihydride RuH(PPh)((*R*,*R*)-cyclohexyldiamine) and Ruthenium Monohydride RuHCl(PPh)((*R*,*R*)-cyclohexyldiamine): Active Catalyst and Catalyst Precursor for the Hydrogenation of Ketones and Imines

Kamaluddin Abdur-Rashid, Alan J. Lough, and Robert H. Morris

Organometallics, 2000, 19 (14), 2655-2657 • DOI: 10.1021/om000231e



Ruthenium Dihydride $RuH_2(PPh_3)_2$((*R*,*R*)-cyclohexyldiamine) and Ruthenium Monohydride $RuHCl(PPh_3)_2$((*R*,*R*)-cyclohexyldiamine): Active Catalyst and Catalyst Precursor for the Hydrogenation of Ketones and Imines

Kamaluddin Abdur-Rashid,* Alan J. Lough, and Robert H. Morris*

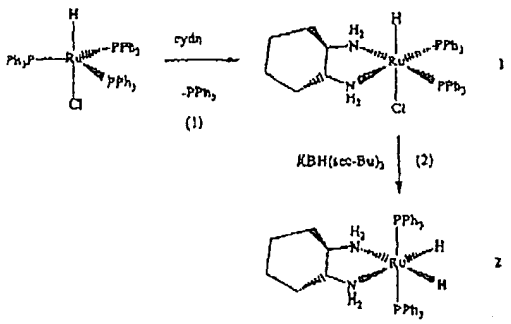
Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada

Received March 16, 2000

Summary: The new monohydride $RuHCl(PPh_3)_2$(R,R-cydn), with base added, and dihydride $RuH_2(PPh_3)_2$-(R,R-cydn), in the absence of base, catalyze the hydrogenation of a wide variety of ketones and some imines at 3 atm of H_2 and 20 °C with high turnover numbers. The mechanism is thought to involve the concerted dihydrogen transfer from cis hydride and N–H groups to the substrate followed by heterolytic dihydrogen splitting.

Noyori and co-workers have reported $RuCl_2(PPh_3)_3$/diamine and $RuCl_2$(diphosphine)(diamine) systems, which are precursors for the generation of what appears to be some of the most active catalysts for the homogeneous and asymmetric hydrogenation of ketones in a 2-propanol/base mixture.[1–3] They suspected that monohydride or dihydride species were the active and selective catalysts in these systems, but they were unable to isolate and characterize these (see footnote 16 of ref 3). In related work they[4,5] and others[6] have provided evidence that the bifunctional Ru–H/N–H motif, a hydride and amine coordinated cis on ruthenium(II), plays an important role in the hydrogenation of ketones and imines by transfer of hydrogen from 2-propanol or $[HNEt_3][HCO_2]$. Our interest in ruthenium hydride and dihydrogen chemistry[7–9] and in protonic–hydridic NH···HM bonds[10,11] led us to study the nature of the ruthenium hydrides that might be present in the Noyori $RuCl_2(PPh_3)_3$/diamine/KOH/2-propanol catalytic system.

Scheme 1



This has led to the discovery that the dihydride $Ru(H)_2$-$(PPh_3)_2$(cydn) (2; cydn = (*R*,*R*)-cyclohexyldiamine) is a very active ketone and imine hydrogenation catalyst, while the monohydride complex Ru(H)(Cl)$(PPh_3)_2$(cydn) (1) is inactive. Ruthenium dihydrides $RuH_2(L)(PPh_3)_3$ (L = H_2, N_2,[12] vacant site[13]) are catalysts for the hydrogenation of cyclohexanone in THF and the transfer hydrogenation of cyclopentanone from 2-propanol solvent. To the best of our knowledge, catalysts based on ruthenium dihydride complexes with two amino ligands are unprecedented.

When an equimolar mixture of $RuHCl(PPh_3)_3$ and cydn in tetrahydrofuran is stirred at room temperature under a nitrogen atmosphere, the substituted complex $RuHCl(PPh_3)_2$(cydn) (1) is formed quantitatively (Scheme 1, eq 1).[14] A similar reaction with ethylenediamine yields $RuHCl(PPh_3)_2$(en), as will be described elsewhere. The ^1H and $^{31}P\{^1H\}$ NMR spectra are consistent with a structure containing mutually cis hydride and phosphorus nuclei. The structure of 1 as shown in Scheme 1 has been confirmed in a preliminary X-ray diffraction study.

(1) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495–497 and references therein.
(2) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417–10418.
(3) Ohkuma, T.; Doucet, H.; Pham, T.; Mikami, K.; Korenaga, T.; Terada, M.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 1086–1087.
(4) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102.
(5) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478.
(6) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588.
(7) Abdur-Rashid, K.; Gusev, D.; Lough, A. J.; Morris, R. H. *Organometallics* **2000**, *19*, 834–843.
(8) Fong, T. P.; Forde, C. E.; Lough, A. J.; Morris, R. H.; Rigo, P.; Rocchini, E.; Stephan, T. *J. Chem. Soc., Dalton Trans.* **1999**, 4475–4488.
(9) Lough, A. J.; Morris, R. H.; Ricciuto, L.; Schlets, T. *Inorg. Chim. Acta* **1998**, *270*, 238–246.
(10) Lough, A. J.; Park, S.; Ramachandran, R.; Morris, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 8356–8357.
(11) Abdur-Rashid, K.; Gusev, D. G.; Landau, S. E.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 11826–11827.
(12) Linn, D. E.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 2969–2974.
(13) Aranyos, A.; Csjernyik, G.; Szabo, K. J.; Backvall, J. E. *Chem. Commun.* **1999**, 2131–2132.
(14) 1: THF (2 mL) was added to $RuHCl(PPh_3)_3$ (300 mg, 0.31 mmol) and (*R*,*R*)-*trans*-cyclohexyldiamine (36 mg, 0.32 mmol) and the mixture stirred for 6 h under nitrogen. The resulting solution was filtered and hexanes (10 mL) added to the filtrate, precipitating a yellow solid. Yield: 224 mg, 94%. ^1H NMR (δ): −17.99 (t), $^2J_{HP}$ = 25.7 Hz, 1H (RuH); 0.45 ppm (br), 2H (NH); 2.38 ppm (br), 2H (NH). $^{31}P\{^1H\}$ NMR (δ): 70.6 (s). IR: 1987 cm^{-1}.

10.1021/om000231e CCC: $19.00
Publication on Web 06/09/2000

Table 1. Catalytic Hydrogenations Using $RuH_2(PPh_3)_2$(*R,R*-cydn) (2) and H_2 Gas[a]

Entry	Substrate	S:C ratio	% Conversion	Time (hr)
1		5000	100	<12
2		5000	100	<8
3		5000	100	<8
4		3600	100	<12
5		4000	100	<12
6		5000	100	<12
7		3600	100	<12
8		5000	87	48
9		500	100	<4
10		280	66	48

[a] Neat substrate except for entries 3, 9, and 10, where benzene was used as the solvent. The product of entry 3 is exclusively the allyl alcohol PhCH=CHCH(OH)Me.

In the presence of catalytic amounts of a base such as sodium hydroxide or sodium isopropoxide under H_2 gas (3.5 atm) at 20 °C, complex **1** (1:base = 1:10) facilitates the efficient hydrogenation of neat ketones and imines to alcohols and amines, respectively (results similar to those of Table 1). In the absence of a base, no hydrogenation was observed, clearly demonstrating that the hydrido chloro species **1** is not the true catalyst.

When a mixture of **1** (50 mg, 65 μmol), acetone (4 mg, 67 μmol), and potassium isopropoxide (7 mg, 65 μmol) in C_6D_6 (0.7 mL) was stirred under hydrogen gas (3.5 atm) for 30 min, the ^1H NMR spectrum showed complete conversion of the ketone to 2-propanol and the presence of the novel dihydride species $Ru(H)_2(PPh_3)_2$(cydn) (**2**). The pure, bright yellow dihydride was prepared by stirring equimolar amounts of **1** and potassium tri-*sec*-butylborohydride in tetrahydrofuran for 12 h under a nitrogen atmosphere at room temperature (Scheme 1, eq 2) and then isolated.[15] The triplet at −18.3 ppm with J_{HP} = 27 Hz for the hydride in the ^1H NMR spectrum and the singlet at 67.2 ppm in the $^{31}P\{^1H\}$ NMR spectra of this complex in C_6D_6 are consistent with trans phosphines and cis hydrides. The single-crystal X-ray structure of the complex is shown in Figure 1.[16] The complex is chiral and approximately C_2 symmetric. The two Ru−H bond lengths are 1.53(2) and 1.62(3) Å. The Ru(1)−N(2) bond length of 2.284(2) Å is longer than that

(15) **2**: THF (2 mL) was added to **1** (200 mg, 0.27 mmol) and potassium tri-*sec*-butylborohydride (200 mg of 1 M solution) and the mixture stirred for 6 h under nitrogen. The resulting mixture was filtered and evaporated to dryness, and the solids were extracted with diethyl ether (10 mL). The ether solution was concentrated to 2 mL and hexanes (5 mL) added, precipitating a bright yellow solid. Yield: 142 mg, 74%. ^1H NMR (δ): −18.25 ppm (t, $^2J_{HP}$ = 27.0 Hz, 2H (RuH); 2.04 ppm (d), 2H (NH). $^{31}P\{^1H\}$ NMR (δ): 67.2 ppm (s).

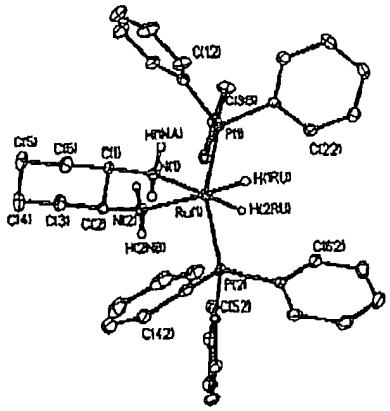


Figure 1. Molecular structure and atomic numbering of complex **2**.

of Ru(1)−N(1) (2.225(3) Å). The RuH···HN distances of 2.8−3.4 Å are too long for significant hydrogen bonding in the solid state. The solid state (Nujol) infrared spectrum of **2** shows two sharp ν_{Ru-H} peaks at 1833 and 1844 cm^{-1} and four sharp ν_{NH} signals in the range 3266−3337 cm^{-1}, also in keeping with a lack of intramolecular hydrogen bonding.

A sealed solution of complex **2** in benzene-d_6 under deuterium gas resulted in the rapid disappearance (within 5 min) of both the NH (2.04 ppm) and hydride (−18.3 ppm) chemical shifts. A series of four triplets at −18.25, −18.23, −18.22, and −18.20 ppm with J_{HP} = 27 Hz in the hydride region of the ^1H NMR spectrum is observed after a 60% decrease in the intensity of the hydride signal. These are due to some of the isotopomers of **2** with one hydride, one deuteride, and with zero to four deuterium atoms in place of the diamine N−H. The rapid H/D exchange observed for both the hydrides and NH moieties when a solution of **2** is exposed to D_2 gas is suggestive of an equilibrium between dihydride and dihydrogen tautomers where the dihydrogen species is too low in concentration to be detected (see eq 6, Scheme 2). Such a mechanism has been proposed for H/D exchange in iridium hydride−amine complexes[17] and has been observed directly for osmium hydride−thiol/dihydrogen−thiolate complexes.[18] No deuteration of either the hydride or NH moieties is observed for complex **1**. The dihydrogen tautomer would be disfavored in this case because the hydride in **1** is less basic, being trans to chloride.

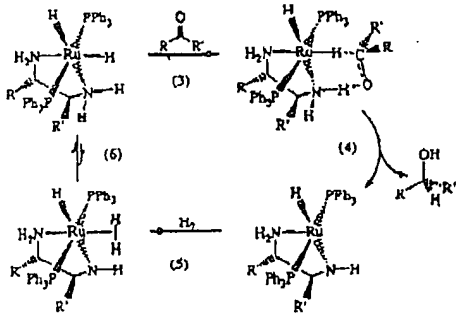
Complex **2** readily catalyzes the hydrogenation of neat ketones to the alcohols under 3 atm of H_2 gas at 20 °C without the addition of a base. For example, neat acetophenone (4.1 g, 34 mmol) was quantitatively hydrogenated to (*S*)-phenethyl alcohol (60% ee) in less than 8 h by use of catalyst **2** (5 mg, 0.0068 mmol).

(16) Crystals of $C_{43}H_{46}N_2P_2Ru$ (**2**) were obtained by layering a diethyl ether solution of the complex with hexanes: M_r = 741.82, monoclinic, space group $P2_1$, a = 8.9595(2) Å, b = 17.7941(6) Å, c = 112.1757(4) Å, β = 103.688(2)°, V = 1885.99(10) Å^3, d = 1.306 g cm^{-3}, Z = 2, T = 150(1) K, 17 210 reflections collected, $R(F)$ = 0.0369 and $R_w(F^2)$ = 0.0648 for 7972 independent reflections.

(17) Koelliker, R.; Milstein, D. *J. Am. Chem. Soc.* **1991**, *113*, 8524−8525.

(18) Schlaf, M.; Morris, R. H. *J. Chem. Soc., Chem. Commun.* **1995**, 625−626.

Scheme 2



Benzene was used as the solvent for the α,β-unsaturated ketone, and the product was exclusively the allyl alcohol. The same selectivity for the ketone over the olefin was reported by Okhuma et al.[2] Our study demonstrates that deactivated and sterically congested ketones such as *tert*-butyl methyl ketone (pinacolone) can also be readily hydrogenated using this procedure. The high conversions shown for the dialkyl ketones are unprecedented and attest to the enhanced activity of these catalysts under the current conditions. The hydrogenation of the aldimine and the ketimine in benzene by use of **2** also proceeded under notably mild conditions (Table 1).

One equivalent of acetophenone reacts with **2** in C_6D_6 in the absence of dihydrogen to give an intermediate currently under study. When the resulting solution was then exposed to H_2 gas, the ^1H NMR spectrum shows the presence of phenethyl alcohol and regenerated **2**.

These observations would be consistent with the proposed mechanism shown in Scheme 2. The first steps in the catalytic cycle (eqs 3 and 4) involves the concerted transfer of the hydride to the carbonyl carbon and NH proton to the oxygen as proposed also for the RuH(η^6-arene)(NH_2LNTs) catalysts.[4,5] Steps 5 and 6 are proposed on the basis of the H/D exchange results mentioned above.

This direct hydrogenation mechanism, in which the dihydride catalyst is regenerated from H_2 gas, differs significantly from the transfer hydrogenation process reported for the series of RuH(η^6-arene)(NH_2LNTs) complexes, in which a hydrogen-donor solvent such as an alcohol or triethylammonium formate is required for the regeneration of the monohydride catalyst. However, in both of these classes of complexes, the presence of a *cis*-M–H···H–N bifunctional motif seems to be a key feature for the activity of these catalysts.

Acknowledgment. This work was supported by a grant to R.H.M. from the NSERC of Canada and a loan of ruthenium(III) chloride from Johnson Matthey Ltd.

Supporting Information Available: Text giving complete characterization data for complexes **1** and **2** and X-ray crystallographic tables for complex **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM000231E

D4

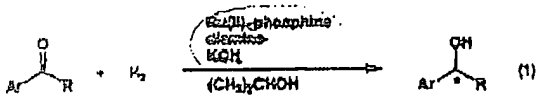
Practical Enantioselective Hydrogenation of Aromatic Ketones

Takeshi Ohkuma, Hirohito Ooka, Shohei Hashiguchi, Takao Ikariya, and Ryoji Noyori*,†

ERATO Molecular Catalysis Project
Research Development Corporation of Japan
1247 Yachigusa, Yakusa-cho, Toyota 470-03, Japan

Received November 29, 1994

Enantioselective hydrogenation of prochiral ketones to optically active secondary alcohols is among the most fundamental subjects in modern synthetic chemistry.[1] BINAP–Ru(II) complex catalysts [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (1)] have proved extremely efficient for the asymmetric hydrogenation of functionalized ketones,[1,2] which results in the industrial production of synthetic intermediates of antibiotic carbapenems[2a,3] and antibacterial Levofloxacin.[4] Rate enhancement and stereochemical control are effectively accomplished by coordination of the functional group to the catalytic Ru center. BINAP–Ru catalysts, though displaying a very wide scope, are unable to hydrogenate simple ketones that lack heteroatoms anchoring the Ru metal. This paper discloses a new and very practical catalyst system that effects enantioselective hydrogenation of the simple aromatic ketones in eq 1. This asymmetric synthesis compares well with existing procedures for catalytic enantioselective reductions.[5–7]



Phosphine–Ru(II) complexes are normally not very active as catalysts for hydrogenation of acetophenone.[8] The activity of $RuCl_2[P(C_6H_5)_3]_3$ was remarkably enhanced with the addition of 1 equiv of ethylenediamine and a >2.8 mM solution of KOH in 2-propanol. The turnover frequency (TOF, defined as moles of the product per mole of the catalyst per hour) of the reduction with $RuCl_2[P(C_6H_5)_3]_3$ alone was less than 5, while the use of the present system led to a TOF of 6700 ([Ru] = 0.28 mM in 2-propanol, $Ru:NH_2(CH_2)_2NH_2:KOH$ = 1:1:20, substrate to catalyst (S/C) mole ratio =5000, 3 atm of H_2, 28 °C). The rate is highly sensitive to the pressure of hydrogen. Thus, the initial TOFs attained at 1 atm (S/C = 500) and 50 atm (S/C = 10 000) were 880 and 23 000, respectively. This hydrogenation proceeds smoothly even at −20 °C. Both the organic and inorganic bases are required. Screening of the diamine ligands suggested that at least one primary amine end is necessary. KOH could be replaced by $(CH_3)_2CHOK$. 2-Propanol is the solvent of choice. The reaction in methanol, ethanol, or *tert*-butyl alcohol is much slower, while THF, dichloromethane, and toluene are not usable.

Although a transition metal complex–base combined system in 2-propanol has frequently been used for transfer hydrogenation of ketones,[7,9] this reductive transformation is a result of net hydrogenation. Under the above standard conditions, acetophenone absorbed H_2 smoothly to give 1-phenylethanol; in the absence of H_2, little alcoholic product was obtainable (TOF < 7). Interestingly, addition of ethylenediamine suppresses the nonhydrogenative reduction (TOF = 70) that occurs in 2-propanol containing $RuCl_2[P(C_6H_5)_3]_3$ and KOH. The absence of transfer hydrogenation was confirmed by the deuterium-labeled experiment. Thus, the Ru-catalyzed reaction in the presence of ethylenediamine and KOH in $(CH_3)_2CDOH$ (S/C = 500, 3 atm of H_2, 28 °C) gave only nondeuterated 1-phenylethanol in >99% yield. No acetone was formed. $(CH_3)_2CDOH$ was recovered without any change. The smooth reaction of benzophenone excluded the possibility of hydrogenation via an enol intermediate.

Encouraged by the marked activity of the new Ru catalyst system in hydrogenation of the simple ketonic substrate, we then examined the asymmetric version. The hydrogenation of 1′-acetonaphthone with a catalyst system consisting of $RuCl_2$[(*S*)-binap](dmf)$_n$,[10] (*S,S*)-1,2-diphenylethylenediamine [(*S,S*)-3],[11] and KOH (1:1:2 mole ratio) in 2-propanol (S/C = 500, 4 atm of H_2, 28 °C, 6 h) afforded (*R*)-1-(1-naphthyl)ethanol in 97% ee and in >99% yield. The high degree of enantioface differentiation is a result of the synergetic effects of the chiral diphosphine and diamine. Replacement of the *S,S* diamine by the *R,R* enantiomer under otherwise identical conditions gave the *R* alcohol in only 14% ee. A combination of the (*S*)-BINAP–Ru complex and achiral ethylenediamine or achiral $RuCl_2[P(C_6H_5)_3]_3$ and (*S,S*)-3 provided the *R* product in 57 and 75% ee, respectively.

† Permanent address: Department of Chemistry, Nagoya University, Chikusa, Nagoya 464-01, Japan.

(1) Recent reviews: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; Chapter 2. (b) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; Chapter 1. (c) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysts*; VCH: Weinheim, 1993.

(2) (a) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187–208. (b) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1989; Vol. 5, pp 115–198. (c) Noyori, R. *Science* **1990**, *248*, 1194–1199. (d) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350. (e) Noyori, R. *CHEMTECH* **1992**, *22*, 360–367.

(3) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

(4) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631.

(5) (a) Bakos, J.; Tóth, I.; Heil, B.; Markó, L. *J. Organomet. Chem.* **1985**, *279*, 23–29. (b) Chan, A. S. C.; Landis, C. R. *J. Mol. Catal.* **1989**, *49*, 165–173. (c) Zhang, X.; Taketomi, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 3318–3319.

(6) For hydroboration and hydrosilylation, see: (a) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039–2044. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. (c) Brunner, H.; Becker, R.; Riepl, G. *Organometallics* **1984**, *3*, 1354–1359. (d) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500–508.

(7) For transfer hydrogenation, see: (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051–1069. (b) Evans, D. A.; Nelson, S. G.; Gagné, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800–9801. (c) Genêt, J.-P.; Ratovelomanana-Vidal, V.; Pinel, C. *Synlett* **1993**, 478–480. (d) Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett.* **1993**, *34*, 6897–6898. (e) Gamez, P.; Dunjic, B.; Fache, F.; Lemaire, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1417–1418. (f) Krasik, P.; Alper, H. *Tetrahedron* **1994**, *50*, 4347–4354.

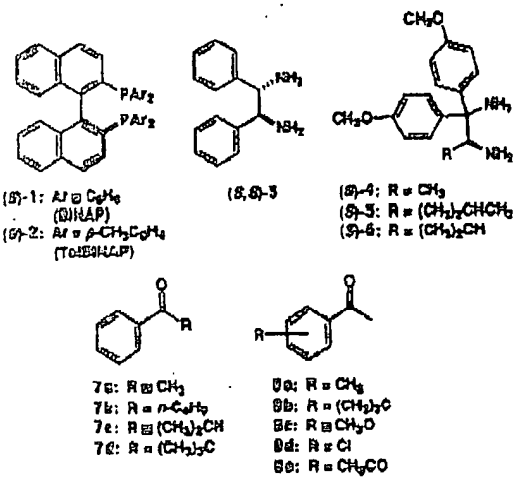
(8) (a) Bennett, M. A.; Matheson, T. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 4, pp 931–965. (b) Tsuji, J.; Suzuki, H. *Chem. Lett.* **1977**, 1085–1086. (c) Grey, R. A.; Pez, G. P.; Wallo, A. *J. Am. Chem. Soc.* **1981**, *103*, 7536–7542. (d) Watanabe, Y.; Ohta, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2441–2444. (e) Hayashi, Y.; Komiya, S.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1984**, 1363–1366. (f) Sánchez-Delgado, R. A.; Valencia, N.; Márquez-Silva, R.-L.; Andriollo, A.; Medina, M. *Inorg. Chem.* **1986**, *25*, 1106–1111. (g) Halpern, J. *Pure Appl. Chem.* **1987**, *59*, 173–180. (h) James, B. R.; Pacheco, A.; Rettig, S. J.; Thorburn, I. S.; Ball, R. G.; Ibers, J. A. *J. Mol. Catal.* **1987**, *41*, 147–161. (i) Suarez, T.; Fontal, B. *J. Mol. Catal.* **1988**, *45*, 335–344. (j) Lau, C. P.; Cheng, L. *Inorg. Chim. Acta* **1992**, *195*, 133–134.

(9) For Ru-catalyzed transfer hydrogenation, see: (a) Bäckvall, J.-E.; Chowdhury, R. L.; Karlsson, U.; Wang, G.-Z. In *Perspectives in Coordination Chemistry*; Williams, A. F., Floriani, C., Merbach, A. E., Eds.; Verlag Helvetica Chimica Acta: Basel, 1992; pp 463–486. (b) Chowdhury, R. L.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1991**, 1063–1064. (c) Bhaduri, S.; Sharma, K.; Mukesh, D. *J. Chem. Soc., Dalton Trans.* **1993**, 1191–1199.

(10) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1–13.

(11) (a) Mangeney, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255–257. (b) Pikul, S.; Corey, E. J. *Org. Synth.* **1993**, *71*, 22–29.

0002-7863/95/1517-2675$09.00/0



A variety of aromatic ketones can be hydrogenated enantioselectively by the BINAP–Ru(II)–diamine–inorganic base combined catalyst system, where the diamines **3**–**6**[11,12] act as the most effective chiral controllers. Table 1 lists some representative examples. Hydrogen pressure does not affect the enantioselectivity. The extent of the enantioselectivity appears to be delicately influenced by the structures of the diamine auxiliaries as well as the substituents in the substrates. In general, use of (*S*)-BINAP and an *S* diamine affords the *R*-configurated alcohol product, whereas the *R*–*R* configurational combination gives the *S*-enriched alcohol. In the reaction of alkyl phenyl ketones **7**, the enantioselectivity was noticeably increased by increasing the bulkiness of the alkyl group from methyl to primary alkyls to isopropyl. Pivalophenone (**7d**), however, was far less reactive. Introduction of an alkyl, methoxy, or chloro substituent to the meta or para position of acetophenone tends to increase the degree of enantioselection. The ketones *m*-**8** and *p*-**8** are reduced with higher enantioselectivity than unsubstituted acetophenone (**7a**) irrespective of the electronic properties of the substituent. The hydrogenation of ortho-methylated and -chlorinated acetophenone, *o*-**8a** and *o*-**8d**, proceeded with a high stereoselectivity. The methoxy compound *o*-**8c** was unreactive, however. Both 1′- and 2′-acetonaphthone displayed an excellent enantioselectivity. The hydrogenation of α-tetralone gave the corresponding alcohol in 100% yield but in at most 59% ee. The application of the Horeau effect[13] allows the synthesis of chiral diols of a very high enantiomeric purity. Thus, while the hydrogenation of para-substituted acetophenone was achieved in 91–96% optical yield, the reaction of *p*-diacetylbenzene (**8e**) with the (*S*)-BINAP–Ru complex and *S* diamine (*S*)-**6** produced nearly enantiomerically pure (*R*,*R*)-*p*-bis(1-hydroxyethyl)benzene in 85% yield in addition to the meso diol in 15% yield. Notably, β-keto esters, the best substrates for the standard BINAP–Ru(II)-catalyzed hydrogenation,[1–4] are inert in the present reaction conditions.

In conclusion, a BINAP–Ru(II) complex–chiral diamine–KOH ternary system acts as a very practical catalyst for enantioselective hydrogenation of simple aromatic ketones. BINAP (**1**)[14] and chiral diamine **3**[11] are now commercially available, while the 1,2-diamines **4**–**6** and their analogues are readily obtainable from amino acids.[12] The reaction can be conducted easily on a preparative scale with an S/C ratio up to 5000 and a substrate concentration as high as 30% in 2-propanol.[13] The hydrogenation takes place smoothly at room temperature at 1–8 atm of H_2, while the reaction occurs very rapidly under high pressure. The workup procedure is simple; in most cases the product is obtainable by direct distillation of the reaction mixture.

Table 1. Enantioselective Hydrogenation of Aromatic Ketones Catalyzed by a BINAP–Ru(II) Complex–Chiral Diamine–KOH System[a]

ketone substrate[b]	chiral element: phosphine	chiral element: diamine	conditions: H_2, atm	conditions: time, h	alcohol product: % yield[c]	alcohol product: % ee[d]	alcohol product: config[e]
7a	(*S*)-**1**	(*S*)-**5**	4	3	>99	87	*R*
7b	(*S*)-**1**	(*S*)-**4**	4	3	>99	90	*R*
7c	(*S*)-**2**	(*S*)-**6**	8	6	>99	95[f]	*R*
o-**8a**	(*S*)-**2**	(*S*,*S*)-**3**	4	5	>99	94	*R*
o-**8d**	(*S*)-**2**	(*S*,*S*)-**3**	50	3	>99	94	*R*
m-**8c**	(*R*)-**1**	(*R*)-**6**	8	3	99	88	*S*
m-**8d**	(*S*)-**2**	(*S*)-**6**	8	1	96	90[g]	*R*
p-**8a**	(*R*)-**1**	(*R*)-**6**	4	3	>99	91	*S*
p-**8b**	(*S*)-**2**	(*S*,*S*)-**3**	4	1.5	>99	96[h]	*R*
p-**8c**	(*R*)-**1**	(*R*)-**6**	4	3	>99	92	*S*
p-**8d**	(*S*)-**2**	(*S*)-**6**	8	16	>99	94[i]	*R*
p-**8e**	(*S*)-**2**	(*S*)-**6**	4	1.5	98[j]	>99[k]	*R*,*R*
1′-NpCOCH$_3$	(*S*)-**1**	(*S*,*S*)-**3**	4	6	>99	97	*R*
1′-NpCOCH$_3$[l]	(*S*)-**1**	(*S*,*S*)-**3**	8	24	>99	95	*R*
2′-NpCOCH$_3$	(*S*)-**2**	(*S*)-**6**	1	18	99	95[m]	*R*
2′-NpCOCH$_3$	(*S*)-**2**	(*S*)-**6**	50[n]	3	98	97[m]	*R*

[a] Reaction was carried out at 11–30 °C using a 1.4 M solution of substrate (5.0 mmol) in 2-propanol. Substrate:Ru:diamine:KOH = 500:1:1:2. [b] Np = naphthyl. [c] Determined by GC and 200-MHz ^{1}H NMR analysis. [d] Determined by HPLC analysis using a DAICEL CHIRALCEL OB column (eluent, 10:90 2-propanol–hexane; flow rate, 0.5 mL/min) unless otherwise specified. [e] Determined by sign of rotation. [f] DAICEL CHIRALPAK AS column (3:97 2-propanol–hexane). [g] CHIRALCEL OJ column (5:95 2-propanol–hexane). [h] HPLC analysis of its acetate using a CHIRALPAK AS column (hexane). [i] A 3:97 2-propanol–hexane mixture as eluent. [j] *dl*:*meso* = 85:15. [k] HPLC analysis of its diacetate using a CHIRALPAK AS column (5:95 2-propanol–hexane). [l] A 30-g-scale reaction. For details, see footnote 15 and supplementary material. [m] CHIRALPAK AS column (5:95 2-propanol–hexane). [n] At −22 °C.

Supplementary Material Available: Full experimental procedure, $[\alpha]_D$ values of the reaction products, and analytical data (mp, $[\alpha]_D$, ^{1}H NMR, IR, and elemental analysis) of compound (*S*)-**5** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA943864R

(12) Wey, S.-J.; O'Connor, K. J.; Burrows, C. J. *Tetrahedron Lett.* **1993**, *34*, 1905–1908. Diamine (*S*)-**5** was prepared according to this method (see also supplementary material).

(13) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055–1059.

(14) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1989**, *67*, 20–32.

(15) Diamine (*S*,*S*)-**3** (7.5 mg, 0.035 mmol) and a 0.5 M 2-propanol solution of KOH (140 μL, 0.070 mmol) were added to 2-propanol (10 mL), and the mixture was degassed by freeze–thaw cycles. To this solution was added $RuCl_2[(S)\text{-binap}](dmf)_n$[10] (33.1 mg, 0.035 mmol), and the resulting mixture was sonicated for 10 min and used as a catalyst. A solution of 1′-acetonaphthone (30.0 g, 176 mmol) in 2-propanol (90 mL) was subjected to freeze–thaw cycles. These two solutions were transferred to a glass autoclave, and then, hydrogen was pressurized to 8 atm. The solution was vigorously stirred at 28 °C for 24 h. After the reaction, the solvent was removed under reduced pressure, and the residue was distilled to give (*R*)-1-(1-naphthyl)ethanol (27.90 g, 92% yield, 95% ee), bp 98–101 °C/0.5 mmHg, $[\alpha]^{25}_D$ +75.8° (*c* 0.99, ether) (lit.[16] $[\alpha]^{25}_D$ +82.1° (*c* 1.0, ether)). The yield determined by ^{1}H NMR was >99%.

(16) Thoisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374–2378.

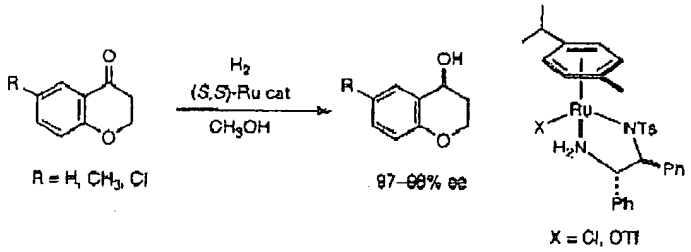
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

The Hydrogenation/Transfer Hydrogenation Network: Asymmetric Hydrogenation of Ketones with Chiral □-Arene/*N*-Tosylethylenediamine–Ruthenium(II) Catalysts

Takeshi Ohkuma, Noriyuki Utsumi, Kunihiko Tsutsumi, Kunihiko Murata, Christian Sandoval, and Ryoji Noyori

J. Am. Chem. Soc., **2006**, 128 (27), 8724-8725• DOI: 10.1021/ja0820989 • Publication Date (Web): 15 June 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 31 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 06/15/2006

The Hydrogenation/Transfer Hydrogenation Network: Asymmetric Hydrogenation of Ketones with Chiral η^6-Arene/*N*-Tosylethylenediamine−Ruthenium(II) Catalysts

Takeshi Ohkuma,‡ Noriyuki Utsumi,§ Kunihiko Tsutsumi,§ Kunihiko Murata,§ Christian Sandoval,† and Ryoji Noyori*,†

Department of Chemistry and Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan, Division of Chemical Process Engineering, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan, and Central Research Laboratory, Technology and Development Division, Kanto Chemical Co., Inc., Soka, Saitama 340-0003, Japan

Received March 27, 2006; E-mail: noyori@chem3.chem.nagoya-u.ac.jp

Asymmetric transfer hydrogenation (ATH) with organic reducing agents catalyzed by transition metal complexes is mechanistically linked with asymmetric hydrogenation (AH) using molecular hydrogen because both reactions commonly involve metal hydride species.[1,2] However, most of the existing chiral catalysts are effective for only one of these reactions.[3−5] We have long conjectured that certain chiral metal complexes can be made to catalyze both ATH and AH by switching reaction parameters so that the conditions can tolerate acid/base-sensitive substrates. In this context, the extensive mechanistic investigation on the Ru-catalyzed ATH[6,7] has led us to rationally explore an effective AH of unfunctionalized ketones. We disclose here that chiral η^6-arene/*N*-tosylethylenediamine−Ru(II) complexes, known as excellent catalysts for ATH,[8] can be used for AH as well. This discovery provides a long-sought method for enantioselectively hydrogenating simple ketones under nonbasic or acidic conditions.[9]

The blue arrows in Figure 1 illustrate the pathway of ATH of aromatic ketones with 2-propanol catalyzed by the chiral Ru chloride **1** (X = Cl) and an alkaline base.[6,7] The strong base is required for the irreversible elimination of HCl from **1** forming the 16e Ru amide complex **2**. Dehydrogenation of 2-propanol by **2** gives the RuH species **3**, which in turn hydrogenates Ar(R)C=O forming chiral Ar(R)CHOH with recovery of **2**. These ketone/alcohol redox processes occur via a Ru−H−C−O−H−N six-membered pericyclic transition structure. When the reaction starts with preformed **2** as catalyst,[8] no additional base is necessary, but the presence of an acid totally diminishes its catalytic activity. Under such conditions, no ketone reduction takes place under a H_2 gas atmosphere. However, the pink arrows in Figure 1 suggest the possibility of AH using the same Ru catalysts simply *by switching the conditions from basic to acidic*. The key is the generation of the cationic Ru species **4** by ionization of **1**. An alternative method is the protonation of the amido ligand of **2** to prevent dehydrogenation of secondary alcohols. The resulting cationic 16e amino Ru complex **4** (solvate) can accept reversibly a H_2 molecule to form the η^2-H_2 complex **5**, whose deprotonation leads to RuH **3** as a common reductive species.

We selected 4-chromanone (**6a**) as substrate, for which no practical AH methods exist (Figure 2).[10] The difficulty arises from the cyclic planar structure and the relatively high acidity of C(3)-H_2 caused by the oxygen atom.[11−13] The mechanism-based catalytic scenario in Figure 1 was first investigated by using the 18e RuCl complex, (*S,S*)-**8a**, with a substrate-to-catalyst molar ratio (*S*/*C*) of 3000 ([**6a**] = 0.3 M, [**8a**] = 0.10 mM in a silanized glass vessel,

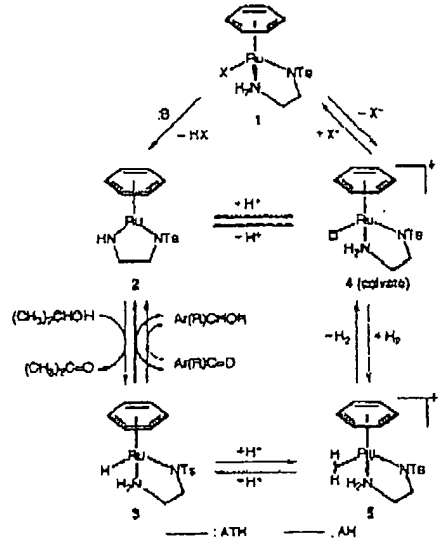


Figure 1. Mechanism of asymmetric transfer hydrogenation (ATH) and asymmetric hydrogenation (AH) of aromatic ketones catalyzed by chiral η^6-arene/*N*-tosylethylenediamine−Ru complexes. Substituents in the arene and ethylenediamine ligands are omitted for clarity.

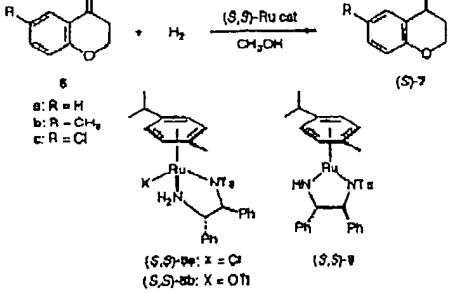


Figure 2. Asymmetric hydrogenation of 4-chromanones.

10 atm, 30 °C, 15 h). We anticipated that ionization of **8a** in a polar solvent would directly generate a catalytic Ru cation (**1** → **4**). In fact, although no reaction took place in 2-propanol (ϵ = 20; the best solvent for ATH[5,8]), hydrogenation in more polar ethanol (ϵ = 25) or methanol (ϵ = 33) gave (*S*)-**7a** in 7% yield (93% ee) and 34% yield (97% ee), respectively. Reaction in methanol at 60 °C and 50 atm increased the yield to 99% (97% ee). As expected, addition of 1 equiv of $(n\text{-}C_4H_9)_4NCl$ to **8a** (*S*/*C* = 3000, methanol,

‡ Nagoya University.
§ Hokkaido University.
† Kanto Chemical Co.

10.1021/ja0620369 CCC: $33.50

Table 1. Asymmetric Hydrogenation of 4-Chromanones Catalyzed by Chiral Ru Complexes[a]

				conditions		(*S*)-7[d]	
ketone	cat.	S/C[b]	additive[c]	H_2, atm	T, °C	% yield	% ee
6p	(*S,S*)-8a	3000		10	30	34	97
6q	(*S,S*)-8a	3000		10	60	64	95
6a	(*S,S*)-8a	3000		50	60	99	97
6r	(*S,S*)-8b	3000		10	60	100	97
6a	(*S,S*)-8b	7000		100	60	100	96
6a	(*S,S*)-9	7000	1.0 TfOH	10	60	60	96
6a[e]	(*S,S*)-9	1000	1.0 TfOH	17	36–57	99	98
6a	(*S,S*)-9	3000	1.0 HBF_4	10	60	99	97
6a	(*S,S*)-9	3000	0.7 $Yb(OTf)_3$	15	50	98	95
6b	(*S,S*)-8b	1500		10	60	95	98
6c	(*S,S*)-8b	1000		10	60	100	98

[a] Unless otherwise stated, reactions were conducted using a 0.3–1.0 M solution of 6 and a 0.1–3.5 mM solution of 8 or 9 in methanol in a silanized glass vessel. The reaction time was 15 h. [b] Substrate/catalyst molar ratio. [c] Molar equiv to Ru. [d] Determined by NMR, the sign of rotation, and chiral HPLC analysis. [e] A 2.4 kg scale reaction using a 2.0 M solution of 6a in a 20 L SUS autoclave for 8 h.

30 °C, 10 atm, 15 h) retarded the reaction to afford (*S*)-7a with 92% ee in only 6% yield.

This AH procedure, though viable, remains unoptimized because the Ru–Cl bond in the precatalyst is not fully dissociated in alcohols. The concentration of the cationic amino Ru complex 4 can be maximized by using a more ionizable precatalyst 1 (X = weakly nucleophilic anion) or by combining the 16e amido Ru complex 2 and an appropriate acid. Notably, the operation of a specific acid/base catalysis requires careful adjustment of the acidity and basicity of the reaction medium to retain a smooth metal–ligand bifunctional catalytic cycle (Figure 1). Pure alcoholic solvents are unable to protonate 2.[8] Strong acid additives facilitate this step, but hamper the deprotonation of 5 and also decoordinate the ethylenediamine ligand from Ru.

The best solution to this problem was provided by invention of the chiral Ru triflate (*S,S*)-8h, which could be obtained simply by adding CF_3SO_3H (TfOH) to (*S,S*)-9[8] in CH_2Cl_2 at 0 °C. In methanol, the Ru triflate precatalyst is cleanly converted to an ion pair acting as an ideal AH catalyst. An equimolar mixture of (*S,S*)-9 and TfOH in methanol was also usable. TfOH could be used in slight excess but not large excess. Thus, when the simple ketone 6a was hydrogenated in methanol under 10 atm of H_2 with *S/C* = 3000 in a silanized glass vessel ([6a] = 1.0 M, [8b] = 0.33 mM, 60 °C, 15 h), (*S*)-7a was obtained in 100% yield and 97% ee (Table 1). The reaction with *S/C* of 7000 took place smoothly at 100 atm. The hydrogenation was accomplished even on a 2.4 kg scale in 8 L of methanol, giving (*S*)-7a with 98% ee in 99% yield. Now less polar alcohols may be used in place of methanol, though the reaction is somewhat slower. TfOH was the best acid to activate (*S,S*)-9, but other non-nucleophilic acids can be employed as well. For example, an equimolar mixture of (*S,S*)-9 and HBF_4·$O(CH_3)_2$ or $Yb(OTf)_3$ in methanol catalyzed the hydrogenation of 6a at 10 atm giving (*S*)-7a in 97% ee in high yield. The results of AH of some 4-chromanone derivatives 6 are listed in Table 1.

The reaction mixture retains a yellow color throughout the hydrogenation. This implies that the amide complex (*S,S*)-9 (purple) is mostly protonated to the amino compounds under the steady-state catalytic conditions. Reduction does not proceed without H_2, indicating that this is a net hydrogenation using H_2 gas. Alcohols are involved in the catalytic cycle, but only as proton sources and bases, not as reducing agents. The sense and degree of enantioselection are the same as those observed in ATH[13] because both AH and ATH involve a common chiral RuH intermediate possessing an *R* configuration at Ru.[8]

In summary, chiral η^6-arene/*N*-tosylethylenediamine–Ru(II) complexes are excellent catalysts not only for ATH but also for AH of aromatic ketones. Various base-sensitive ketonic substrates can be enantioselectively hydrogenated by this method.[14]

Acknowledgment. This work was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (JSPS) (Nos. 14GS0214 and 15350079), the New Energy and Industrial Technology Development Organization (NEDO), and the Sumitomo Foundation.

Supporting Information Available: Preparative methods and properties of chiral Ru complex 8b, procedures for asymmetric hydrogenation of chromanones, NMR, GC, and HPLC behavior, and $[\alpha]_D$ values of products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Noyori, R.; Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5356–5362.

(2) (a) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 6.1. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 1. (c) Ohkuma, T.; Noyori, R. In *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; pp 25–69. (d) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 5.1. (e) Brown, J. M. *J. Organomet. Chem.* **2004**, *689*, 4006–4015. (f) Halpern, J. In *Asymmetric in Synthesis*, Morrison, J. D., Ed.; Academic Press: New York, 1994; Vol. 5, Chapter 1. (g) *Mechanisms in Homogeneous Catalysis*; Heaton, B., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 1.

(3) BINAP/Ru complexes effect AH and ATH of unfunctionalized carboxylic acids. See: (a) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174–5175. (b) Brown, J. M.; Brunner, H.; Leitner, W.; Rose, M. *Tetrahedron: Asymmetry* **1991**, *2*, 331–334.

(4) Achiral (cyclopentadienone)Ru carbonyl complexes effect hydrogenation (34 atm, 145 °C, *S/C* = 1000) and transfer hydrogenation (2-propanol with KOH, *S/C* = 6000) of acetophenone. See: (a) Blum, Y.; Czarkie, D.; Rahamim, Y.; Shvo, Y. *Organometallics* **1985**, *4*, 1459–1461. (b) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090–1110.

(5) (Diphosphine)(α-picolylamine)$RuCl_2$ complexes catalyze both hydrogenation and transfer hydrogenation, depending on the phosphine ligands, under basic conditions: (a) Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2005**, *127*, 8288–8289. (b) Baratta, W.; Herdtweck, E.; Siega, K.; Toniutti, M.; Rigo, P. *Organometallics* **2005**, *24*, 1660–1669. (c) See also: Naud, F.; Malan, C.; Spindler, F.; Rüggeberg, C.; Schmidt, A. T.; Blaser, H. U. *Adv. Synth. Catal.* **2006**, *348*, 47–50.

(6) (a) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931–7944. (b) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201–2237.

(7) (a) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478. (b) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588.

(8) Haak, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285–288.

(9) ATH reaction of ketones is assumed mostly by 2-propanol containing a strong base or a formic acid/triethylamine mixture as reducing agent. See: (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061. (c) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393–406.

(10) A BINAP/aminophosphine–Ir complex catalyzes AH of 6a at >50 atm and 90 °C, giving 7a in 93% ee and 89% yield, but only with *S/C* of 200: Zhang, X.; Takemoto, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 3318–3319.

(11) BINAP/1,4-diamine–Ru complexes are effective for AH of 1-tetralone but not 6: Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* **2004**, *6*, 2681–2683.

(12) For AH with $RuH(\eta^1\text{-}BH_4)$(binap)(1,2-diamine) under slightly basic conditions, see: Ohkuma, T.; Koizumi, M.; Muñiz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508–6509.

(13) ATH of 6a using a formic acid/triethylamine mixture catalyzed by (*S,S*)-8a with *S/C* = 500 at 30 °C for 17 h afforded (*S*)-7a with 97% ee but in only 37% yield.

(14) For AH of simple ketones under basic conditions, see: (a) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73. (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022. (c) Sandoval, C. A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503.

JA062098J

D2

Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid−Triethylamine Mixture

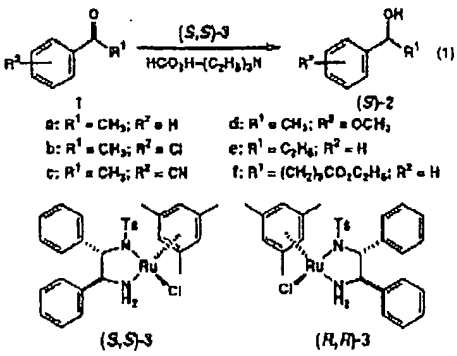
Akio Fujii, Shohei Hashiguchi, Nobuyuki Uematsu, Takao Ikariya, and Ryoji Noyori*,†

ERATO Molecular Catalysis Project
Research Development Corporation of Japan
1247 Yachigusa, Yakusa-cho, Toyota 470-03, Japan

Received December 7, 1995

Catalytic transfer hydrogenation of ketones to alcohols with 2-propanol sometimes offers an attractive alternative to the reaction with molecular hydrogen because of the favorable properties of the organic hydrogen source.[1] However, when the method is applied to the asymmetric version,[2−4] it encounters inherent chemical problems. Even if the reduction proceeds with excellent kinetic enantioface discrimination, the occurrence of the reverse process originating from the structural similarity of the hydrogen donor and product, both being secondary alcohols, frequently deteriorates the enantiomeric purity of the chiral product.[1−5] In addition, the unfavorable ketone:alcohol equilibrium ratio often prevents a high conversion. Use of formic acid[6] in place of 2-propanol presents an obvious possibility to solve these problems. This hydrogen donor, viewed as an adduct of H_2 and CO_2, must effect the reaction irreversibly with truly kinetic enantioselection and, in principle, 100% conversion. However, its use in asymmetric ketone reduction has remained elusive because of the lack of suitable transition metal catalysts.[7] We have found that Ru(II) complexes modified with an arene and a chiral *N*-tosylated 1,2-diamine[2] serve as efficient catalysts for the asymmetric reduction using a 5:2 formic acid−triethylamine azeotropic mixture under mild conditions.

The reduction of acetophenone (**1a**) to 1-phenylethanol (**2a**) was selected as the model reaction (eq 1: $R^1 = CH_3$; $R^2 = H$). Screening experiments revealed that the catalyst of choice was the chiral Ru complex, (*R*)-RuCl[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-mesitylene) [(*S*,*S*)-**3**] or the enantiomer [(*R*,*R*)-**3**], which was prepared by reacting $[RuCl_2(\eta^6\text{-mesitylene})]_2$, (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine (TsDPEN), and triethylamine (Ru atom:TsDPEN:triethylamine molar ratio = 1:1:2) in 2-propanol at 80 °C for 1 h.[2,8] Reaction using a 2 M solution of **1a** in a 5:2 formic acid−triethylamine azeotrope[9] containing (*S*,*S*)-**3** [substrate/catalyst (S/C) mole ratio = 200:1, 28 °C, 20 h] gave (*S*)-**2a** in 98% ee and in >99% yield.[10] The reaction at 60 °C proceeded 8−10 times faster with a 2% decrease in ee. This reduction can be conducted even in a 10 M solution (ca. 50% v/v concentration) and with S/C = 1000:1. The reactivity and enantioface-differentiation ability of the Ru complex **3** result from the compromise between the steric and electronic properties of the arene ligand and the chiral diamine auxiliary. The reactivity decreases in the order benzene > *p*-cymene and mesitylene > hexamethylbenzene as ligand, while mesitylene or *p*-cymene displays a better enantioselection than unsubstituted benzene. The presence of the NH_2 terminus in the TsDPEN auxiliary is crucially important. The $NHCH_3$ analogue showed a comparable enantioselectivity but with much lower reactivity; the $N(CH_3)_2$ derivative gave very poor reactivity and stereoselectivity.



As shown in Table 1, a range of aromatic ketones can be reduced to the secondary alcohols with a high chemical yield and a satisfactory ee. Various acetophenone derivatives, **1b**−**d**, and the higher analogues, **1e** and **1f**, as well as acetonaphthones (**4** and **5**) can be used as substrates. The absence of the reverse process was confirmed by exposure of enantiomerically pure (*S*)- and (*R*)-**2a** to the reaction conditions with or without ketone **1b**. The irreversibility of the reaction results in a series of benefits. Enantioselectivity of the reduction using a 2 M solution of **1a** with (*S*,*S*)-**3** is kept consistently high (*S*:*R* = 99:1) throughout the reaction until completion. With a 2 M solution of **1a** in 2-propanol, the yield of (*S*)-**2a** cannot be high (at most 63%) for thermodynamic reasons, the calculated **2a**:**1a** equilibrium ratio being ca. 70:30.[2] Furthermore, the new reaction system reduced *p*-methoxyacetophenone (*p*-**1d**), among the most notorious substrates, to (*S*)-*p*-**2d** in 97% ee and >99% yield, presenting a significant improvement from the result in 2-propanol (70% ee and 33% yield after 6 h).

Although various para-substituted acetophenones are consistently convertible to the alcohols with >90% ee (Table 1), the

† Permanent address: Department of Chemistry, Nagoya University, Chikusa, Nagoya 464-01, Japan.

(1) Reviews: (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* 1992, *92*, 1051−1069. (b) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* 1994, 1007−1017.

(2) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* 1995, *117*, 7562−7563.

(3) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. *J. Chem. Soc., Chem. Commun.*, in press.

(4) (a) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* 1991, *74*, 232−240. (b) Chowdhury, R. L.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* 1991, 1063−1064. (c) Genêt, J.-P.; Ratovelomanana-Vidal, V.; Pinel, C. *Synlett* 1993, 478−480. (d) Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett.* 1993, *34*, 6897−6898. (e) Gamez, P.; Dunjic, B.; Fache, F.; Lemaire, M. *J. Chem. Soc., Chem. Commun.* 1994, 1417−1418. (f) Gamez, P.; Fache, F.; Lemaire, M. *Bull. Soc. Chim. Fr.* 1994, *131*, 600−602. (g) Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* 1995, *6*, 705−718. (h) Krasik, P.; Alper, H. *Tetrahedron* 1994, *50*, 4347−4354. (i) Yang, H.; Alvarez, M.; Lugan, N.; Mathieu, R. *J. Chem. Soc., Chem. Commun.* 1995, 1721−1722.

(5) In certain cases, the reverse process is slow. See: (a) Evans, D. A.; Nelson, S. G.; Gagné, M. R.; Muci, A. R. *J. Am. Chem. Soc.* 1993, *115*, 9800−9801. (b) Gao, J.-X.; Ikariya, T.; Noyori, R. *Organometallics*, in press.

(6) (a) Watanabe, Y.; Ohta, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* 1982, *55*, 2441−2444. (b) Nakano, T.; Ando, J.; Ishii, Y.; Ogawa, M. *Tech. Rep. Kansai Univ.* 1987, *29*, 69−76.

(7) For the use for asymmetric saturation of olefinic substrates, see: (a) Brunner, H.; Kunz, M. *Chem. Ber.* 1986, *119*, 2868−2873. (b) Brown, J. M.; Brunner, H.; Leitner, W.; Rose, M. *Tetrahedron: Asymmetry* 1991, *2*, 331−334. (c) Leitner, W.; Brown, J. M.; Brunner, H. *J. Am. Chem. Soc.* 1993, *115*, 152−159. (d) Saburi, M.; Ohnuki, M.; Ogasawara, M.; Takahashi, T.; Uchida, Y. *Tetrahedron Lett.* 1992, *33*, 5783−5786.

(8) (*S*,*S*)-**3**: orange solid; mp 218.6−222.5 °C dec; ^{1}H NMR ($CDCl_3$) 2.24 (s, 3H, CH_3), 2.38 (s, 9H, CH_3), 3.69 (dd, 1H, *J* = 11.2 and 11.2 Hz, $CHNH_2$), 3.79 (d, 1H, *J* = 11.2 Hz, CHNTs), 3.99 (dd, 1H, *J* = 9.3 and 11.2 Hz, NH), 4.19 (brd, 1H, *J* = 9.3 Hz, NH), 5.30 (s, 3H, arom), 6.65−6.93 (m, 9H, arom), 7.06−7.15 (m, 3H, arom), 7.35 (d, 2H, *J* = 7.8 Hz, arom). Recrystallization from 99% ethanol afforded crystals of (*S*,*S*)-**3**·H_2O: mp 220.1−222.3 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.58 (s, H_2O), 3.98−4.12 (br, 2H, NH_2). Chemical shifts of other signals were identical with those of (*S*,*S*)-**3**. The molecular structure determined by single-crystal X-ray analysis confirms the *R* configuration at the Ru center[2] (see supporting information).

(9) (a) Wagner, K. *Angew. Chem., Int. Ed. Engl.* 1970, *9*, 51−54. (b) Narita, K.; Sekiya, M. *Chem. Pharm. Bull.* 1977, *25*, 135−140.

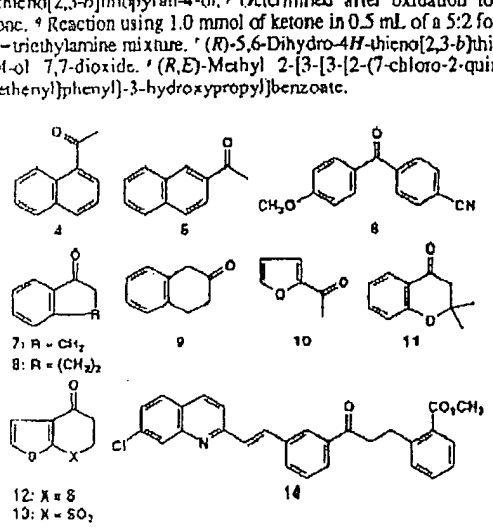
(10) The reaction can conveniently be conducted in an open vessel using a mixture of $[RuCl_2(\eta^6\text{-mesitylene})]_2$ and TsDPEN in a formic acid−triethylamine mixture without isolating **3**.

0002-7863/96/1518-2521$12.00/0

Table 1. Asymmetric Transfer Hydrogenation of Ketones in a Formic Acid–Triethylamine Mixture Catalyzed by a Chiral Ru(II) Complex[a]

			alcohol		
ketone	3, catalyst	time, h	% yield[b]	% ee[c]	config[d]
1a	*S,S*	20	>99	98[e]	*S*
1a	*S,S*	1.5[f]	>99	96[e]	*S*
1a[g]	*S,S*	60	>99	98[e]	*S*
m-1b	*S,S*	21	>99	97[e]	*S*
p-1b	*S,S*	24	>99	95[e]	*S*
p-1c	*S,S*	14	>99	90[h]	*S*
m-1d	*S,S*	50	>99	98	*S*
p-1d	*S,S*	60	>99	97	*S*
1e	*S,S*	60	96	97	*S*
1f	*S,S*	90	99	95[i]	*S*[i]
4	*S,S*	60	93	83	*S*
5	*S,S*	22	>99	96[k]	*S*
6[l]	*S,S*	60	54	66[d]	*S*[m]
7	*S,S*	48	>99	99	*S*
8	*S,S*	48	>99	99	*S*
8	*S,S*	6[f]	>99	98	*S*
9	*S,S*	80	70	82[n]	*S*
10	*S,S*	36	>99	98[e]	*S*
11[o]	*S,S*	40	47	97[d]	*S*
12	*R,R*	40	95[p]	99	*R*[q]
13[r]	*R,R*	65	95[r]	98	*R*
14[s]	*R,R*	72	68[r]	92[t]	*R*

[a] The reaction was carried out at 28 °C using a ketone (5.0 mmol) in a formic acid–triethylamine mixture (5:2, 2.5 mL) with S/C = 200. [b] Determined by GLC or 400-MHz ^{1}H NMR analysis. [c] HPLC analysis using a Daicel Chiralcel OB column unless otherwise specified. Details are described in the supporting information. [d] Determined by the sign of rotation of the isolated product. [e] Capillary GLC analysis using a chiral Chrompack CP-cyclodextrin-β-236-M-19 column. [f] Reaction at 60 °C. [g] Reaction using a 10 M solution of the ketone (25 mmol) in a formic acid–triethylamine mixture (2:1, 2.7 mL, 25 mmol) with S/C = 1000. After 12 h, the reducing agent (0.4 mL, 10 mmol) was renewed. [h] Chiralcel OJ column. [i] Chiralcel OD column. [j] Determined after conversion to (*S*)-6-phenylhexahydro-2*H*-pyran-2-one. [k] Chiralpak AS column. [l] THF (1 mL) was added to dissolve the ketonic substrate. [m] Determined by X-ray analysis after condensation with (*R*)-1-(1-naphthyl)ethyl isocyanate. [n] Chiralpak AD column. [o] (*R*)-5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-ol. [p] Determined after oxidation to the sulfone. [q] Reaction using 1.0 mmol of ketone in 0.5 mL of a 5:2 formic acid–triethylamine mixture. [r] (*R*)-5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-ol 7,7-dioxide. [s] (*R,E*)-Methyl 2-[3-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-hydroxypropyl]benzoate.



electron-withdrawing substituents tend to slightly decrease the enantioselectivity. A benzophenone derivative **6**, with electron-accepting and -donating substituents at the para positions, was reduced to (*S*)-*p*-methoxy-*p'*-cyanobenzhydrol in 66% ee,[11] a notable enantiomeric bias corresponding to $\Delta\Delta G^{\ddagger} = 0.95$ kcal/mol. The absolute configuration of the major enantiomer was determined by X-ray crystallographic analysis after condensation with (*R*)-1-(1-naphthyl)ethyl isocyanate. Thus, the enantiomeric bias of the asymmetric reduction appears to be generated by both steric and electronic factors.

Asymmetric reduction of 1-indanone (**7**) and 1-tetralone (**8**) is now best effected by this method to give 1-indanol and 1-tetralol in 99% ee and >99% yield. Furthermore, the 2-furyl ketone **10** and oxacyclic ketone **11** were reduced to the corresponding alcohol[12] with a high ee. The reaction of the sulfur-containing ketones **12** and **13** in the presence of (*R,R*)-**3** led to the *R* alcohols in >98% ee, which serve as key intermediates for the synthesis of MK-0417, an excellent carbonic anhydrase inhibitor.[13]

This transfer hydrogenation is selective for a keto function.[7] The reduction of the multifunctionalized ketone **14** catalyzed by (*R,R*)-**3** gave the desired *R* benzylic alcohol, an intermediate in the synthesis of L-699,392 (LTD_4 antagonist),[14] in 92% ee without affecting the olefinic bond, halogen atom, quinoline ring, and ester function.

Under the catalytic conditions, formic acid decomposes into H_2 and CO_2 to a substantial extent. However, gaseous hydrogen participates little in the alcohol formation. First, an attempted reaction of **1a** with hydrogen gas in a 2:1 mixture of acetic acid (a nonreducing formic acid analogue) and triethylamine under otherwise identical conditions (20 atm, [**1a**] = 2 M, S/C = 200, 28 °C, 20 h) gave (*S*)-**2a** in only 75% ee and 5% yield. The presence of formic acid (10 equiv with respect to Ru) did not show any marked effect. Furthermore, reaction of **1a** with a 5:2 formic acid–triethylamine mixture under a D_2 atmosphere (65 atm, HCO_2H:D_2 mole ratio = 1:29, S/C = 200, 28 °C, 40 h) formed (*S*)-**2a** in 98% ee and 99% yield, in which 0.08D and 0.18D (0.06D/hydrogen) were incorporated at the C(1) and C(2) positions (^{2}H NMR analysis).

In summary, this work presents the first successful use of a formic acid–triethylamine mixture for asymmetric transfer hydrogenation of ketones. This method overwhelms the energetic requirement of the reduction process, where an unfavorable thermodynamic balance is expected with 2-propanol as the hydrogen source. Thus, the asymmetric reaction proceeds under truly kinetic control to completion with a much higher substrate concentration (2–10 M) than in 2-propanol (<0.1 M).

Acknowledgment. We thank Professor Shin-ichi Inoue of Aichi Institute of Technology and Professor Masashi Yamakawa of Kinjo Gakuin University for valuable discussions, Professor Masafumi Hirano of Tokyo University of Agriculture and Technology for analysis of gas in the reaction mixture, and Miss Mieko Kunieda of JRDC for skillful analytical assistance.

Supporting Information Available: Experimental procedures for the transfer hydrogenation, HPLC or GLC behavior, and $[\alpha]_D$ values of the products and data of single-crystal X-ray analysis of (*S,S*)-**3**·H_2O and (*S*)-(*p*-methoxyphenyl)(*p'*-cyanophenyl)methyl (*R*)-*N*-1-(1-naphthyl)ethylcarbamate (39 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA954126L

(11) For asymmetric hydrosilylation and hydroboration of benzophenone derivatives, see: (a) Peyronel, J.-F.; Fiaud, J.-C.; Kagan, H. B. *J. Chem. Res. Miniprint* **1980**, 4057–4080. (b) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153–9156.

(12) Majerić, M.; Gelo-Pujić, M.; Šunjić, V.; Lévai, A.; Sebök, P.; Timár, T. *Tetrahedron: Asymmetry* **1995**, *6*, 937–944.
(13) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763–769.
(14) King, A. O.; Corley, E. G.; Anderson, R. K.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; Xiang, Y. B.; Belley, M.; Leblanc, Y.; Labelle, M.; Prasit, P.; Zamboni, R. J. *J. Org. Chem.* **1993**, *58*, 3731–3735.